IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Tommy Ekstrom
Serial No. : 09/367,950
Filed : August 18, 1999
Appeal No.: 2007-1154
Title : NEW USE

Art Unit : 1617
Examiner : Jennifer M. Kim
Conf. No. : 4952

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RE-TRANSMITTAL OF INTERVIEW SUMMARY

On November 13, 2007, Applicant filed via EFS-WEB an Interview Summary Following Board Decision of August 28, 2007. The version viewable on PAIR shows page 6 as a blank page. Accordingly, Appellant re-submits herewith the entire 12-page document as previously filed.

No fees are believed to be due. Any necessary charges, or any credits, should be applied to Deposit Account No. 06 1050, referencing Attorney Docket No. 06275-188001.

Respectfully submitted,

Date: Nov. 21, 2007

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I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: November 21, 2007

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INTERVIEW SUMMARY FOLLOWING BOARD DECISION OF AUGUST 28, 2007

In *Ex parte* Tommy Ekstrom (hereafter, the "Decision"), the Board reversed the rejection of claims 13, 35, 36, and 42 under the enablement provision of 35 U.S.C. § 112, first paragraph. The Board also found that the rejections under 35 U.S.C. § 103(a) are not in condition for a decision on appeal. Thus, claims 13-15, 17, 18, 20-36, 38, 42, and 43 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Carling, and claims 16 and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Carling, Aberg, and Ryrfeldt.

The Board remanded the application for further consideration on issues of written description, claim interpretation and statutory subject matter before consideration of the outstanding obviousness rejection. The Board also invited Appellant to "take an active role in clarifying the foregoing issues." Decision at page 11. In an effort to engage in a dialog with the Examiner to address the remaining issues, Appellant's representatives Janis Fraser and Allyson Hatton participated in a telephone interview with the Examiner on October 18, 2007 (the "October 18th interview").

Appellant thanks the Examiner for her time and consideration in the October 18th interview with Appellant's representatives. The written description and claim interpretation issues raised by the Board were discussed, and a summary of the interview is provided below.

I. Amendments to the claims.

Appellant's representatives proposed amending the preambles of independent claims 13, 35, 36, and 42[1] to be directed to "prevention OR treatment" instead of "prevention AND treatment." Such amendment would only be to clarify the meaning of the claims and is not to

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[1] The independent claims are as follows:

13. A method of prevention and treatment of asthma symptoms, which comprises
instructing a patient to inhale an effective amount of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;
characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms.

35. A method of prevention and treatment of asthma symptoms, which comprises
instructing a patient to inhale an effective amount of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;
characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a complement to maintenance treatment of the patient's asthma.

36. A method of prevention and treatment of asthma symptoms, which comprises
instructing a patient to inhale an effective amount of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;
characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient, when the patient is expecting to encounter an asthma triggering event, as a preventative measure.

42. A method of prevention and treatment of asthma symptoms, which comprises
instructing a patient to inhale an effective amount of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;
characterized in that the patient is instructed to take a maintenance dose of the composition, and, if the patient experiences asthma symptoms, to inhale additional doses as needed to improve control and provide acute relief.

43. A method of reducing the incidence of acute asthma attacks, which comprises
instructing a patient to inhale an effective amount of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
(b) a second active ingredient which is budesonide;
characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and to reduce the incidence of acute asthma attacks, when the patient experiences an increase in asthma symptoms.

address any of the comments presented in the Decision. Examiner did not agree to this proposal, but indicated that she would consider whether this would be appropriate at this stage of appeal. Appellant would like to address this issue again in a follow-up interview.

II. Related application.

Appellant's representatives brought to the Examiner's attention U.S. Application No. 10/665,240, which is a continuation of the current application. Examiner Kendra Carter mailed a first Office Action in that continuation application on January 30, 2007, rejecting the claims for nonstatutory double patenting, lack of enablement, and obviousness over Carling alone (citing page 4, lines 4-21, and other portions of Carling) or Carling in combination with two other references. The Examiner was also invited to review the response to that Office Action filed July 27, 2007, and any later papers that may become of record in that case.[2] Copies of the papers from this related application can be provided to the Examiner upon request.

III. Written Description.

On the issue of written description in particular, the Board encouraged Appellant to be an active participant and to clearly explain where written descriptive support for the claims is found in the specification. Decision at page 6. The Board stated that the claims do "not appear to contain a literal disclosure of a method wherein a patient is instructed to inhale an effective amount of a composition on demand." The Board asks for support for the phrases "instructing a patient to inhale" and "instructing a patient to inhale the composition on demand" which were initially added to claim 13 in Appellant's reply mailed April 18, 2001. The phrase "instructing a patient to inhale" appears in each independent claim (claims 13, 35, 36, 42, and 43), and the phrase "instructing a patient to inhale the composition on demand" appears in independent claims 13, 35, 36, and 43.

[2] A new Office Action finally rejecting the claims of that application for nonstatutory double patenting and obviousness was mailed to Appellant on October 18, 2007.

Appellant notes that the words "instructing the patient" do not appear explicitly in the specification. However, the concept is necessarily imbedded in the entire disclosure such that the reader would certainly understand it to be there. This derives from (a) the nature of the invention and (b) what is made explicit in the specification. Each of these points was addressed in the interview, as summarized below.

(a) Nature of the invention. The nature of inhalable asthma medications is such that either the patient self-administers them, or, if the patient is unable to do so (*e.g.*, the patient is a child or an elderly person), the patient's caregiver administers them to the patient. Generally a patient would not visit a hospital or doctor's office to receive routine, daily treatment with the sort of drugs recited in the present claims. The combination therapy described in the claims includes formoterol (a beta-agonist) and budesonide (a steroid). This combination is a prescription medicine, and therefore it will be prescribed (as for any prescription medicine) with some sort of instructions regarding dosage and frequency. This is necessarily true for any prescription drug that is to be self-administered, and particularly one such as budesonide or formoterol that has potentially dangerous side effects when used in too high dosage or too frequently. Thus, the doctor has to instruct the patient in how much to use, and when. If the drug is one supplied from an inhaler, then the doctor instructs the patient regarding the amount of the drug to inhale (*e.g.*, one metered dose) and how often (*e.g.*, twice per day, or six times per day, or on demand as determined by the patient).

Any disclosure in the application regarding how often or under what conditions the patient should self-administer the drug necessarily implies disclosure of "instructing the patient" to do exactly that. Without such an instruction, the patient would have no idea what to do with the drug. It is inconceivable that an inhaler containing a potent drug would be given to the patient with no instructions whatsoever.

(b) Explicit language. Explicit language found in the application also indicates that the phrase "instructing the patient" would be understood by one of ordinary skill in the art to be inherently described. Several examples are discussed below.

(1) The specification at page 4, lines 4-5, states that "**in the present invention, it has been found that it is possible for the patient to administer this mixture as often as needed**." It is understood that the patient would receive instruction from some source to self-administer the mixture "as needed," as it would be unreasonable to assume that the patient could decide this on his own for a potentially dangerous drug. The specification at page 4, lines 12-13, also refers to taking the combination "when needed," and describes the "as needed use" as "Pro Re Nata, PRN," a standard term used by physicians in writing prescriptions.[3] This again implies that a physician or other medical personnel will instruct the patient.

(2) The specification at page 4, lines 19-23, states:

> A treatment for patients suffering from respiratory disease, particularly asthma (including allergic conditions, *e.g.*, episodic or intermittent asthma), will therefore be to use the combination formoterol/budesonide for maintenance therapy as well as on an **as needed basis** (for rescue purposes), *e.g.*, for prevention of exercise and/or allergen induced asthma.

This passage conveys that it is up to the patient to decide when the drug is needed, and it is obvious that the details of this treatment would have to be communicated to the person who is self-administering the treatment, *i.e.*, the patient. That would be "instruction."

(3) Example 5 at page 8 describes use of the formoterol/budesonide combination by a hypothetical patient, saying that the patient is on maintenance treatment and additionally uses the same combination either for rescue purposes or "as needed." As the patient would not have decided for himself to administer this drug "as needed," the decision must be based on an "instruction."

(4) Example 6 at page 9 also describes use of the combination by a hypothetical patient, in this case "as sole medication to be taken as needed until the asthma resolves. The highest

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[3] Pro Re Nata is variously defined in the art as meaning, e.g., "as needed" or "on demand." See, e.g., the attached exhibit ("Advances in pain control: cancer and palliative care" *Health News* 7:5-7, 1989), which defines PRN as "on demand" (page 5, second column, second full paragraph).

recommended daily dose will be..." Clearly, the recommendation for the highest daily dose, to be taken "as needed," will come from some source of instruction to the patient.

(5) The specification at pages 1-2 says, "too complicated therapy...may lead to misunderstanding and communication problems between patient and doctor." "Communication" would include what the doctor tells the patient, *i.e.*, the "instructions."

(6) The specification also speaks of "compliance" (meaning compliance with the doctor's instructions) and "patient education." See the specification at page 2, lines 1-2.

These examples all imply instructions.

As the Board also noted, "[a]lthough the exact terms need not be used in haec verba,...the [S]pecification must contain an equivalent description of the claimed subject matter" Lockwood v. American Airlines Inc., 107 F.3d 1565, 1571-1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). As described above, reference in the specification to, for example, treatment regimens and patients and recommended daily doses is description that inherently requires a source of instruction that will teach the patient how to self-administer the combination therapy.

To satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention. See MPEP 2163(I). As exemplified by the passages highlighted above, the description in the specification is sufficient to convey to one of skill in the art at the time the application was filed that Appellant was in possession of the methods as claimed.

At the conclusion of the interview, the Examiner and Appellant's representatives seemed to be in agreement that the claims were supported by adequate written description. The Examiner expressed an intent to discuss the issue with her supervisor and then communicate the U.S. Patent and Trademark Office's position to Appellant's undersigned representative by telephone.

IV. Claim Interpretation

In its Decision, the Board also asked that the Examiner consider how to interpret the claims, particularly in view of the phrases "instructing a patient to inhale" and "instructing a patient to inhale the composition on demand." Decision at page 7. Appellant's representatives addressed this issue with the Examiner during the interview.

The independent claims require that a patient be instructed to inhale a composition containing a mixture of formoterol and budesonide (i) on demand, as determined by the patient, based on the patient's symptoms (claims 13, 35, and 43); (ii) on demand, when the patient is expecting to encounter an asthma triggering event (claim 3b); or (iii) when the patient experiences asthma symptoms, to provide acute relief (claim 42). It is possible that a given patient may act according to the instructions by taking the composition zero times in one day, and twice on another day, and three times on another. If he is instructed to take a regular maintenance dose or doses every day as well as the "on demand" doses, he would take at least that maintenance dose or doses each day and in addition from zero to whatever number the physician stated to be the maximum, depending on his need each day. The patient is the one who determines when the composition is "needed," since the patient is the one who knows when she is about to encounter asthma-inducing conditions or is experiencing symptoms of an asthma attack. As Appellant's representatives pointed out to the Examiner in the October 18th interview, patients had never before been told to take inhaled steroids (such as budesonide) on demand as needed, as determined by the patient, *i.e.*, "on demand." Evidence placed on record during the prosecution of the application indicates that professionals in the field in fact taught the opposite, *i.e.*, not to deviate from a prescribed regimen for steroid-containing therapies. See, *e.g.*, Appeal Brief submitted March 3, 2006, pages 18-21.

Appellant's representatives also noted that it is known in the art that instructions for self-administering drugs can be communicated to patients in many different ways. The patient could simply be told by a doctor or nurse to take a particular number of puffs from the inhaler at any point that he feels the need to do so. Alternatively, the patient could be told to visit a particular website or be given an audio or video recording that communicates this instruction, or he could

be given a hand-written prescription, or a printed or electronic document that explains the treatment. The specification does not limit how the instruction might be delivered, or by whom.

It is Appellant's understanding that the Examiner agrees with the above interpretation of the claim language at issue.

V. Statutory Subject Matter

In the Decision, the Board asked the Examiner to explain whether the claim "constitutes a statutory process." Decision at page 10. Appellant asked the Examiner for an opportunity to discuss this issue by telephone once agreement has been reached that the claims satisfy the written description requirement and after the proper interpretation of the claims has been determined. The Examiner indicated that this would be possible.

Appellant looks forward to hearing from the Examiner regarding the written description and claim interpretation issues, and about scheduling a time for a second interview to discuss the statutory subject matter question raised by the Board.

No fees are believed to be due. Any necessary charges, or any credits, should be applied to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188001.

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HEALTH NEWS

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In this issue, in-depth articles on...

Warts

Shingles

Cancer pain and palliative care

Banishing warts

(I ficky, ficky thee: an old wart charm)

Since the discovery that transmissible viruses cause warts and that some warts may lead to cancer, fresh attention is focussing on their eradication.

Reports about warts date back to antiquity, and even in Roman times physicians suspected that warts might be infectious and sometimes sexually transmitted. Warts are very common and can occur at any age but are especially prevalent among children aged 12 to 16 — perhaps because of their intimacy and the frequency of open scrapes and scratches through which wart infections gain entry. One British study found that about 16 per cent of teenagers had warts on the hands, feet or face.

These somewhat distasteful, flesh-coloured skin protrusions appear on the fingers, face, feet or other parts of the body, including the genitals (where they may be tiny, flat and almost invisible). Some warts persist for years but unless uncomfortable, unsightly or a health risk may be ignored. While most warts are harmless and reasonably inconspicuous, some become exceptionally big, growing several centimetres across. If they occur in a prominent part of the body, such as the face, warts present a cosmetic problem; if on the soles of the feet they may be painful to walk on. Venereal or genital warts may lead to cervical cancer in women (*see the October 1989 issue of* Health News).

Warts are caused by viruses

Warts are due to an invasion of the skin or *mucous membranes* (lining tissues) by viruses known as *papillomaviruses*. These wart viruses were first seen under the electron microscope in the 1950s. Since then, 50 different sub-types of the *human papillomavirus* (HPV) family have been identified, each responsible for warts at specific body sites. Some individual warts contain several strains of *papillomaviruses*.

Quite contagious, these viruses enter the body through small cuts or abrasions in the skin and can be transferred from one body part to another — say, from hands to feet or face — or from person to person. It is possible to become infected by wart viruses from damp towels touched by an infected person or to pick up the foot HPV virus from the floors of changing rooms or showers. Genital warts are spread by sexual contact. Nasal wart viruses can be passed on among cocaine users who snort the drug through a shared holder, sometimes rolled dollar bills.

The amount of wart virus present in an infected area is greatest six to 12 months after infection, gradually declining thereafter, so that warts will usually disappear after a few months to a couple of years. There may be a time lag or "incubation period" of three months or longer between the time of exposure, when the virus enters the skin, and the appearance of a wart. With genital warts, people may have to think back to past sex partners to discover who gave them the infection.

Warts often vanish spontaneously

Most warts start out as small, pinhead-sized bumps that get larger over a few weeks or months, sometimes becoming flecked with little black spots. If cut, they bleed in pinpoint flecks. Warts vary in size and shape but generally have a limited life span. Left alone, most get smaller and disappear within three months to five years with an average vanishing time around two years. Many wart "cures" claim to take 12 weeks — a time span within which some warts would disappear *without* any treatment. How and why warts regress are still debated questions. Possibly the body's immune defences fight off the wart infection. Many wart treatments work by irritating the warts slightly so that they release wart antigen (active ingredient) into the blood, stimulating an immune response — either a cell-mediated (T-cell) response or antibody production. Treating warts in one place may get rid of others elsewhere.

Multiple, large, treatment-resistant warts can become a major problem, especially in people with any kind of immune system weakness or deficiency such as AIDS, those with leukemia or Hodgkin's disease (a type of cancer), people on immunosuppressant drugs (such as organ transplant recipients) and cancer patients undergoing radiation or chemotherapy.

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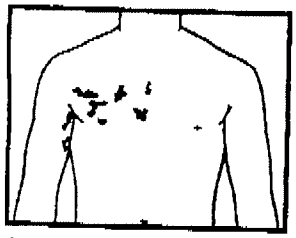
The shingles rash often runs in a narrow strip from the back to the front of the trunk.



Typical Shingles Rash

weeks after the acute shingles phase, *post-herpetic neuralgia* (PHN), occurs in 10 per cent of those over 40 and one half to two thirds of those older than 60 who get shingles. About 80 per cent of those with PHN describe the pain as unpleasant but bearable. The rest find it an agonizing sensation, never letting up except perhaps during sleep, although it's often irritating enough to hinder sleep. The pain can also upset appetite, cause lassitude and diminish sex drive. Many patients complain of *allodynia* (pain on contact with certain stimuli such as the touch of clothing) and *hyperpathia* (prolonged, radiating pain superimposed on the continuous itch). But the pain tends to fade with time, often vanishing in a year or so.

Remedies proposed for post-shingles pain

- *Antidepressants* help many, not because of their antidepressant effect but because the medication can relieve pain (in doses lower than those normally used for depression). It may be necessary to stay on the medication for some weeks to achieve relief.
- *Transcutaneous electrical nerve stimulation (TENS)* often enhances relief.
- *Steroids* (anti-inflammatory agents), such as *triamcinolone*, injected into the painful region may benefit some.
- *Opioid painkillers* do not usually alleviate PHN but may be helpful if all else fails.
- *Early use of sympathetic nerve blockade or local anesthetics* may be helpful but since these methods are elaborate and expensive, and there is little evidence of *long term* benefit, anesthetic remedies are not strongly supported for PHN.
- *Capsaicin*, the pungent element in red peppers and related vegetables (marketed as Zostrix, in a 0.025 per cent preparation), can alleviate PHN and promises relief to some sufferers. Exactly how hot pepper ointment relieves post-shingles pain is unclear but it may deplete pain pathways of substance *P* (a pain transmitter), thus relieving pain. Or the ointment may mimic oil of cloves as its active component is similar to *eugenol* in the popular toothache remedy. However, while the hot pepper ingredient may relieve PHN it can also sting because it stimulates nerve endings. A study conducted at one University of Toronto Pain Clinic found that 39 per cent of those who persevered with hot pepper treatment experienced relief by rubbing the cream onto the painful site four times a day. For over half of the subjects, relief of PHN was rated as "good to excellent." On the down side, one-third of the subjects withdrew from the trial, unable to stand the stinging caused by the pepper cream. A preliminary U.S. study found that 12 out of 14 patients who applied Zostrix to the painful area five times a day for a week, then three times a day for the next three weeks, experienced "substantial" relief. Further studies on pepper cream are planned.* ❑

*Volunteers are needed for future studies on hot pepper treatment of post-shingles pain. If interested, please call (416) 231-5152.

Advances in pain control: cancer and palliative care

Progress in pain control has evolved largely from improvements in cancer care which address both physical and emotional suffering.

Canada is rapidly becoming a world leader in palliative care (which includes the care of incurable and terminal conditions). Many new palliative care units are opening up around the country. But despite a deeper understanding of pain mechanisms, many physicians still prescribe too little pain medication, sometimes because of old fashioned ideas about the need to keep medication to a minimum and irrational fears about addiction.

Pain management gradually improving

In the past, pain medication was mainly prescribed PRN — "on demand" or when pain returned. Today's approach to chronic pain is to prescribe painkillers *around-the-clock*, tailoring doses to achieve continuous relief and prevent pain from surfacing rather than waiting to treat it after it has reappeared. Whatever its cause, pain requires continuous, regular *preventive* therapy instead of permitting panic to build to the point where patients and their families become distraught. Hitting pain early and keeping it down at all times helps to reduce the overall amount of drugs needed and banishes the fear and anticipation which magnify its intensity. Patients are encouraged to gain personal control over pain, sometimes administering drug mixtures themselves in doses that never let pain "break through" or surface. People often feel better when they participate in their own pain control.

Advances in pain management have been largely pioneered by the *British hospice movement*. Hospices for the dying were started within British hospitals during the early 1900s and expanded in the 1950s by pioneers such as Drs. Cicely Saunders and Richard Twycross who established humane principles for *palliative* and *terminal care*. In Canada, the British word "hospice" has been largely replaced by the term "palliative care unit." The hospice concept of total pain management — now accepted world-wide — addresses mental, social and spiritual as well as physical problems. It is based on an analgesic "ladder" system, using non-opioid painkillers first (such as *ASA*/ Aspirin or *acetaminophen*/ Tylenol) followed by mild opioids, such as codeine, then stronger ones.

While poppy derivatives (or their synthetic replacements) remain the mainstay of modern analgesia, other drugs are also used. Pain specialists prefer to use the term *opioid* instead of "narcotic" which has negative connotations. Opioid drugs include natural poppy derivatives (such as opium, codeine, morphine, heroin) and synthetic substances, such as Demerol, which mimic the properties of opium (SEE DRUG TABLE).

Cancer pain

Cancer pain usually originates from tumour expansion, inflammation, invasion of bone and other organs, nerve destruction or as a complication of therapies such as surgery, chemotherapy or radiation. It is often worsened by hopelessness, a sense of disability, depression, isolation, family stress and fear of impending death — aspects that need to be

Some reasons for inadequate pain management

- faulty pain assessment and improper diagnosis;
- patient reluctance to complain and failure of healthcare givers to ask about pain;
- inappropriate or wrong medication given;
- ignorance about the effectiveness and best use of opioids — doses too low and too infrequent;
- medications administered PRN (on request) instead of around the clock, leading to breakthrough pain and anxiety;
- failure to recognize nerve [illegible] (which doesn't respond well to opioids);
- the flawed belief [illegible] the idea that opioid drugs [illegible] until needed;
- "opiophobia" — patient, family and professional fear of addiction to opioid medications;
- fear of breathing problems in patients on opioids [illegible] doses are increased gradually);
- negligence in treating opioid side effects such as nausea, constipation and drowsiness;
- failure to add non-opioid co-analgesics for better pain control.

addressed by healthcare teams. With advanced disease, 60-90 per cent of cancer patients experience severe pain at some point, but only about a third currently receive adequate pain relief. Although cancer pain often responds better than other types of chronic pain to drug therapy, paradoxically it continues to be grossly undertreated despite the fact that the drugs that can control it are freely available and well understood. The World Health Organization (WHO) now regards cancer pain relief as a top priority. Studies conducted in the last decade show that too many physicians and nurses as well as the general public retain the outmoded idea that pain-killing drugs lead to addiction, or that it's a "sin" or a "shame" to resort to opioids because of their link to abuse and crime. In reality, *pain retards recovery* as does the mistaken belief that it's better to resist the need for painkillers or "tough it out."

In Canada, no large epidemiological study has yet been completed on cancer pain management. Word of mouth, anecdotes and small surveys indicate that pain is probably no better managed here than in other countries. One study which may shed light on the problem is scheduled for completion next year. Jointly initiated by the *Canadian, Prince Edward Island, Manitoba* and *Quebec Cancer Societies* and researchers at Toronto's *Clarke Institute of Psychiatry*, the study will involve about 1,500 cancer patients in Quebec, Manitoba and PEI. Preliminary results for PEI indicate that half of those interviewed have had pain at some point since diagnosis. For two thirds of them the pain was worst at the time of surgery; 18 per cent had been in some pain during the week before they were interviewed; and even those taking drugs continued to experience some breakthrough pain, rated as "distressing to excruciating" despite the prescribed medication.

Although many caregivers believe that some cancer pain is inevitable, this is far from true. The British hospice movement claims that good pain control is achievable in the vast majority of cancer sufferers — complete relief in up to 87 per cent, acceptable relief in nine per cent and partial relief in about four per cent of patients. (Other centres report slightly lower success rates, with 80 per cent of cancer patients kept pain-free, 10 per cent reasonably comfortable and the rest only partially controlled.) Pain relief may take a few days to three weeks to achieve.

Most cancer patients find pain tolerable or entirely absent with 30-60 mg doses of morphine (given every four hours), some needing more or doing better on alternate drugs. *Severe, persistent cancer pain* usually demands opioid drugs. Finding the right dose may take time, with a "rescue dose" prescribed for times when pain breaks through. Co-analgesics (non-narcotic painkillers such as anti-inflammatories and antidepressants) are often given together with opioids to enhance relief. If the usual regimen fails, epidural (spinal) or subcutaneous (under the skin) administration may work.

Addiction not a problem in pain patients

Many healthcare professionals fear drug dependency, thinking that pain patients will inevitably request more and more drugs. However, pain patients generally ask for more medication only in order to relieve greater pain not to achieve a drug "high." There is continued difficulty in distinguishing *physical dependence* (which produces withdrawal symptoms such as sweating, shaking and nausea when the drug is suddenly stopped) from *psychological addiction*, which is the craving for a drug "high" — common in substance abusers. Experts repeatedly stress that among pain sufferers opioid use *differs radically* from that of psychological drug addicts. Although some *physical* dependence is usual after taking opioids for a long time, *psychological* dependence hardly ever occurs among pain patients.

Requests for more medication by pain patients generally represent an increase in tumour size or disease progression and greater pain, not drug addiction. The *American Medical Association, American College of Physicians*, the *Canadian Task Force* and the *WHO* repeatedly emphasize that addiction to opioids among pain patients and those with incurable illness is *extremely rare*. If a certain opioid dose works for pain patients they will stick to it without escalating the amount. One University of Toronto pain specialist points out that many pain patients when told to start on opioids accept most reluctantly. "They'd far rather take less or none," he comments, "thinking they should reserve opioids for later when they might need them more." And once they start on opioids, many don't even take the full dose. As the specialist puts it, "I prescribe, they decide (how much to take)."

Another common fear among healthcare workers is *drug tolerance* — habituation to a certain dose and an escalating need for more to achieve the same pain relief. However, experience shows that while some tolerance occurs in pain patients it is usually predictable and the amount of medication needed to quench pain soon stabilizes. Studies show that less than 0.1 per cent of cancer patients become addicted to opioids. And there is evidence that addiction may be equally rare in patients treated for non-malignant pain. One survey of 10,000 burn victims treated with opioids showed not a single case of addiction in previously non-drug-using patients.

Opioid side effects are easily banished

A few common side effects from opioids need to be treated as soon as people start on these painkillers. Constipation (which occurs in about 90 per cent of patients) and various types of nausea (common in 60 per cent of opioid users) gradually wear off but experts suggest that when prescribing opioids, healthcare givers should *also routinely* prescribe a laxative and anti-nauseant.

Constipation can be counteracted by a diet rich in fluids and fibre, the use of stool softeners and stimulant laxatives such as Senokot and Dulcolax (in consultation with a physician).

Nausea and vomiting — common when starting to take opioids — usually disappears in a week or two. It can be offset by anti-emetic medications such as *haloperidol* (Haldol), *prochlorperazine* (Stemetil), *metoclopramide* (Maxeran) and *domperidone* (Motilium). *Dimenhydrinate* (Gravol) is not considered useful for opioid-induced nausea.

Drowsiness, sedation, dizziness and confusion are common in the first three to seven days of opioid therapy but after about a week the brain adjusts to the drug, remaining alert while retaining the analgesic effects. Respiratory failure is unlikely if opioid doses are slowly increased but may occur (in much less than one per cent of patients). It can be reversed by *naloxone* which counteracts the effects of morphine.

Twilight sedation an occasional last resort

Most terminal patients can be kept reasonably pain-free. However, in an extremely small number of cases, when disease is very advanced and pain cannot be well managed by trying all available methods, some units employ "twilight sedation." This highly controversial procedure involves heavy sedation with an opioid plus tranquillizers, sometimes for weeks, until death. Twilight sleep has aroused concerns among health professionals, some of whom believe that it resembles *euthanasia* (mercy killing). However, other experts feel that when, and *only* when, all other options have been exhausted, forcing patients to endure excruciating pain in the last stage of their lives is needless cruelty. Since the patient is not in a coma but can be awakened at any time, the use of twilight sleep is regarded by some as a humane alternative to euthanasia, but it is only used in exceptional cases and only by mutual consent of patient and physician.

Commonly used painkilling drugs

ASA or Aspirin, highly effective for many forms of mild-to-moderate pain, acts by inhibiting the release of prostaglandins (pain-exaggerating body chemicals) and reducing inflammation, for example, arthritis. ASA and its derivatives have the great advantage of being non-sedating, non-addictive and easily available. ASA is increasingly used *together with* opioids to control the pain of bone and other cancers which don't respond to morphine alone. However, unlike opioids (where increasing doses provide more analgesia), there is a "ceiling" on the amount of pain ASA can relieve.

Other non-narcotic drugs useful against some types of pain include *acetaminophen* (Tylenol), anti-psychotics (such as *haloperidol* or Haldol) and anti-inflammatories such as steroids or NSAIDS (non-steroidal anti-inflammatories), some of which — like ASA — are prostaglandin-inhibitors: e.g., *ibuprofen* (Motrin) or *ketoprofen* (Orudis).

The narcotics or opioids, from the Greek meaning "to numb," remain the world's most potent painkillers, ranging from the milder *codeine* to the strongest known analgesics: *morphine, hydromorphone* (Dilaudid) and *heroin* (now legal in Canada for pain treatment). Opioid drugs bind to brain receptors, blocking pain perception. Increasing doses usually bring greater relief. Most opioids can be given by mouth unless the inability to swallow necessitates the rectal, intravenous or sub-lingual (under the tongue) route. New long-acting, slow release forms aid pain relief. For selected patients, a small pump can now continuously infuse tiny opioid doses under the skin giving excellent relief with few complications.

Reactions to opioids vary greatly. Some people can remain active even if taking morphine or other opioids for years while others may feel drowsy and need a stimulant (such as Ritalin/amphetamine) to remain alert. Over-sedation is an occasional problem in those who wish to carry on as usual, but drowsiness usually wears off in a week or two. (In fact, a little drowsiness while inactive helps people to "catnap" and forget their distress.)

The opioid drugs used for pain include:

- *Morphine*: the standard opium derivative against which the effectiveness of all others is measured, now available in a long-acting form (MS. Contin) giving eight to 12 hours pain relief.
- *Hydromorphone* (Dilaudid): a more soluble morphine derivative and the most soluble opioid known (as strong or stronger than heroin), useful for providing a lot of drug in a little fluid. It can be given orally, rectally or injected. (This drug, not available in Britain, has largely replaced the need for heroin in Canada.)
- *Oxymorphone* (Numorphan): about the same strength as morphine, can be taken as rectal suppositories or by injection, giving four hour pain relief.
- *Diamorphine* (heroin): widely used for cancer pain in the U.K. and U.S. but not in Canada, gives slightly quicker-acting but shorter pain relief than morphine.
- *Oxycodone*: a morphine derivative similar to codeine is easy to take as tablets — usually mixed with ASA (in Percodan) or with acetaminophen (in Percocet).
- *Methadone:* a synthetic morphine substitute, well absorbed by mouth with a longer-lasting effect than morphine (sometimes used to help addicts withdraw from narcotics) but may accumulate and produce adverse side-effects.
- *Meperidine* (Demerol) and *anileridine* (Leritine): synthetic morphine substitutes which relieve pain for four hours at best, more likely three hours only.

Co-analgesics that can increase opioid pain relief

Tricyclic antidepressants such as amitriptyline (Elavil) *or imipramine* (Tofranil) can reinforce the effect of opioids often in doses lower than those required for depression. Besides helping to lift depression (common in pain patients), tricyclics also suppress pain and act as sedatives. Known to ease headache, low back and shingles pain, these drugs are especially useful in treating pain from malfunctioning or injured nerves caused by tumour growth, surgery or radiation.

Cortisone and its steroid relatives (anti-inflammatories) can alleviate pain due to nerve injury or inflammation. Besides their anti-inflammatory action, steroids also increase energy, appetite and strength, thereby improving overall well-being. But they cannot be used for very long without adverse side effects.

Anti-convulsants such as *methotrimeprazine* or *carbamazepine* (Tegretol) may help to relieve nerve-root pain, but in a few people Tegretol lowers the white blood cell and platelet count, a side effect that may be problematic in patients undergoing chemotherapy or radiation.

Tranquillizers may enhance analgesia by modifying emotional states and making people feel relaxed, thereby breaking the pain cycle. *Major tranquillizers,* such as the *phenothiazines* (e.g., chlorpromazine, Nozinan) and *minor tranquillizers,* such as *benzodiazepines* (e.g., Diazepam), may increase pain relief. ❑